REMARKS

Claims 1, 22, 40 and 62 have been amended to recite "...an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for human α4β7 integrin..." Support for amended claims 1, 22, 40 and 62 is found, for example, at page 6, lines 4-7.

New claims 80-92 have been added.

Support for new claim 80 is found, for example, in original claims 1, 11 and 12 and at page 17, lines 7-9.

Support for new claims 81 and 82 is found, for example, at page 16, lines 24-25.

Support for new claim 83 is found, for example, at page 17, lines 7-9.

Support for new claims 84-87, 89 and 91 is found, for example, at page 16, lines 27-29.

Support for new claims 88, 90 and 92 is found, for example, at page 15, lines 25-29 and page 16, lines 24-25.

Rejection of Claims 1, 13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62 and 70-79 Under 35 U.S.C. § 112, First Paragraph

Claims 1, 13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62 and 70-79 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. In the Examiner's opinion, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner states that the claims encompass use of an antibody which binds α4β7 from any animal species, but it is unclear as to what species of α4β7 were known in the art other than murine or human. (Office Action, page 3.)

Claims 1, 22, 40 and 62 have been amended to recite "...an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for human α4β7 integrin..." thereby making this objection moot with respect to these claims. Claims 13, 18, 26, 31, 36, 41, 46, 51, 55-60, 62 and 70-79 depend from the amended claims, thereby making the rejection moot with respect to these claims as well.

Rejection of Claims 1, 8-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62-64 and 70-79 Under 35 U.S.C. § 103(a)

Claims 1, 8-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62-64 and 70-79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ponath *et al.* (WO 98/06248) in view of Gordon *et al.* (Reference AS5 of record) or Gordon *et al.* (Reference AT5 of record).

The Examiner states that Ponath *et al.* disclose treatment of ulcerative colitis with humanized LDP-02 antibody, wherein said antibody has the amino acid sequence recited in the claims. The Examiner further states that Ponath *et al.* disclose that the dosage and schedule of administration used would be determined using routine experimentation, that the antibody can be administered in multiple doses, and that the patient can additionally receive steroids or sulfasalazine or other immunosuppressive agents. The Examiner admits that Ponath *et al.* do not disclose the particular claimed administration protocols. (Office Action, page 5.)

The Examiner states that the Gordon *et al.* references disclose that patients with inflammatory bowel disease or ulcerative colitis can be treated with a dose of 3 mg of humanized antibody against an α4 integrin, wherein said dosage is a starting point for future clinical studies. In the Examiner's opinion, a routineer would have started with the 3 mg/kg dosage disclosed by Gordon *et al.* and arrived at the claimed protocols using routine experimentation. The Examiner also cites KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007) as saying that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." (Office Action, pages 5-6.)

Applicants respectfully disagree. The claimed invention is not obvious over the cited references because none of the references either individually or in combination suggests the claimed methods of treatment.

Scope and Content of the Prior Art

Ponath *et al.* describe the LDP-02 antibody and that the humanized immunoglobulin can be administered in an effective amount to inhibit binding α4β7 integrin to a ligand thereof. Ponath *et al.* generally disclose that a suitable dosage for antibodies can be from about 0.1 mg/kg

body weight to about 10.0 mg/kg body weight per treatment. (Ponath *et al.* at page 29, lines 16-30.)

The Gordon *et al.* references merely describe the results of a study in which a single 3 mg/kg dose of the anti-α4 antibody Antegrin™, which binds α4β1 and α4β7 integrins, was administered to patients with ulcerative colitis

Differences Between the Prior Art and the Claims at Issue

Ponath *et al.* do not teach the particular claimed administration protocols. Ponath *et al.* teach that the LDP-02 antibody could be administered to treat ulcerative colitis if provided at an effective dose that falls within a general range.

The combined teachings of Ponath *et al.* and the Gordon *et al.* references, at best, would provide a method for treating ulcerative colitis by administering an antibody at a single dose of 3 mg/kg.

The claims are drawn to methods for treating a human having a disease associated with leukocyte infiltration of mucosal tissues, comprising administering to said human an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for human α4β7 integrin with specific dosages and timing of administration protocols.

Level of Ordinary Skill in the Art

The level of ordinary skill in the art was high.

Secondary Considerations

The present invention provides a therapeutic approach that produces superior efficacy at a lower dose relative to Gordon *et al.*

Gordon *et al.* describes the results of a study in which a single 3 mg/kg dose of the anti-α4 antibody Antegrin™, which binds α4β1 and α4β7 integrins, was administered to patients with ulcerative colitis. Gordon *et al.* reports that treatment resulted in a reduction of the median Powell-Tuck (PT) score from a pre-treatment level of 10 to 7.5 and 6. This is a median reduction of the PT score of 2.5 and 4 after treatment.

The application describes the results of administration of 0.5 mg/kg of LDP-02, which specifically binds the α4β7 complex, to patients with ulcerative colitis. The application discloses that this approach resulted in a median reduction of the PT score of 6. (See, Table 23, page 45). Thus, the specification demonstrates the superior efficacy, as measured by a reduction in the PT score, was achieved using six times less antibody than that used by Gordon *et al.* The application further discloses that similar efficacy was observed as assessed by Endoscopic Severity Score and Mayo Clinic Activity Index.

The claimed invention would not have been obvious to a person of ordinary skill over the teachings of Ponath *et al.* and Gordon *et al.* First, a person of ordinary skill would not combine Ponath *et al.* and Gordon *et al.* because these references relate to antibodies that have different specificities. LDP-02, which binds the α4β7 complex, and Antegren™, which binds α4 (*i.e.*, α4β1 and α4β7), are not functionally equivalent. Evidence is provided by Schweighoffer *et al.* (Reference AV3 of record) and Poldolsky (Reference AS2 of record) which shows that ACT-1, the mouse antibody that was humanized to produce LDP-02, augments cell adhesion to VCAM, while anti-α4 antibodies inhibit this type of adhesion (See, Schweighoffer *et al.* at Abstract and Figure 6 and Podolsky *et al.* at Figure 1 and Figure 4). Because of the different biological properties of antibodies that bind the α4β7 complex and those that bind α4, a person of ordinary skill would not consider the antibodies to be equivalents and would not look to Gordon *et al.* for dosing information or even a starting point to experiment with LDP-02.

Even if, for argument alone, a person was induced to experiment by the teachings of Ponath *et al.* and Gordon *et al.*, he could only have reasonably expected to achieve results that are similar to those disclosed in Gordon *et al.* There is no basis in the prior art for the person of ordinary skill to expect that superior results could be obtained. Thus, the person of ordinary skill could not have predicted or reasonably expected that superior efficacy, as measured by a reduction in the PT score, would be achieved using six times less antibody than in Gordon *et al.*

The Examiner's reference to the KSR case is acknowledged, however Applicants' do not recognize the relevance of the cited portion of the case to the facts of this case. Applicants are not claiming a method for improving an existing ***device***. KSR does however, endorse patentability when greater than expected results are obtained. KSR, 127 S. Ct. at 1739-1741.

Thus, Claims 1, 8-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62-64 and 70-79 are not obvious in light of Ponath *et al.* (WO 98/06248) in view of Gordon *et al.* (Reference AS5 of record) or Gordon *et al.* (Reference AT5 of record). Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____

Kristin A. Connarn
Registration No. 57,025
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

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